REMARKS

Reconsideration and withdrawal of the rejections to the application is respectfully requested in view of the remarks herein and the attached Declaration under 37 C.F.R. §1.132 of Dr. Jean-Christophe Audonnet.

Claims 17-28 and 38-49 are pending in this application. The Examiner is thanked for indicating that the double patenting rejection and the rejection under 35 U.S.C. §112, second paragraph, have been withdrawn.

THE REJECTIONS UNDER 35 U.S.C. §103 ARE OVERCOME

Claims 17-32 and 38-49 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over Haanes *et al.* (U.S. Patent No. 5,753,235 or 5,804,197), in view of Paoletti *et al.* (U.S. Patent No. 5,843,456). The rejection is traversed.

The claims are directed to a recombinant CHV comprising and expressing at least one heterologous nucleotide sequence encoding rabies virus G protein. As discussed in the Amendment filed on March 7, 2003, the cited art does not teach or suggest a recombinant CHV comprising and expressing at least one heterologous nucleotide sequence encoding rabies virus G.

To the contrary, both Haanes references relate only to the construction of a canine herpesvirus expression vector. Haanes do not teach which genes to use in the expression vector. The Office Action asserts that Paoletti involves the use of the HA or F gene of canine distemper virus, G gene of rabies virus, and the VP2 gene of canine parvovirus **in an analogous viral vector vaccine**. (Emphasis added.) Applicants maintain that Paoletti is non-analogous art.

The Office Action cites Esposito *et al.* and Tartaglia *et al.* as representative examples of the state of the art. It is respectfully submitted that although Esposito and Tartaglia describe several viral vectors for use in vaccines, neither reference states, or provides any evidence that would lead the skilled artisan to believe, that these different vectors are interchangeable.

Esposito states the problems associated with the different vector types in the paragraph bridging pages 197 and 198, in particular, that:

> "[t]hey all have complex *in vivo* replication demands, less-than-perfect virulence characteristics, and some undesirable host range traits. They all require further research to define and optimized these characteristics. For example, the persistence of adenoviruses in lymphatic tissues and herpes viruses in neural tissues and the progressive course of vaccinia virus injection in immunocompromised individuals must be studied further. We must better

> understand the consequences of specific deletion mutation in these vector viruses, such as those caused during the insertion of heterologous DNA. Such mutations may affect virulence, tropism, and host range, as well as immunogenicity."

In that passage, Esposito advocates further research on each type of vector virus, especially in view of the different effects each has on the host, for example, persistence in different tissue types.

Contrary to providing evidence that the various viral vector vaccines are analogous, Esposito draws attention to their differences, stating on page 230 that:

> "[n]o one virus or family of viruses identified has ideal characteristics for use as the substrate for all infectious vectored virus vaccines. Differences in the desired usage of vaccines are such that different vectors may be envisioned in different circumstances. Hence, the feasibility for using any virus with a large enough genome to carry heterologous genes must be considered. In this regard, **the herpesviruses offer several unique advantages**...".

This section of Esposito goes on to describe the strong, cell-mediated immune response evoked by herpesviruses, as well as strong, long-lasting humoral responses, which result in continuous or intermittent (via recrudescence) stimulation of the immune system of the subject receiving a herpesvirus-vectored vaccine. This is in contrast to the effects of poxvirus-based vaccines described in this reference.

Tartaglia focuses on the use of poxviruses as vaccine candidates, with only a few paragraphs of discussion regarding adenoviruses and herpesviruses. At best, Tartaglia mentions that these viruses have been employed as vaccine candidates, but certainly makes no statement or insinuation that they are interchangeable with the poxviruses that are the main subject of the reference. In fact, Tartaglia cautions against the use of adenoviruses and herpesviruses as recombinant vaccine candidates, stating on page 1990 that they "should be evaluated carefully with respect to their oncogenic potential since members of both virus families have been shown to affect cell growth and function." In that regard, Tartaglia actually teaches away from the instant invention.

As further evidence that immunization with different recombinant viral vaccines does not produce analogous results, references by Gilbert *et al.* (1987; Virus Research 7:49-67) and Wardley *et al.* (1992; J. Gen. Virol. 73:1811-1818) are attached. Gilbert describes a recombinant vaccinia virus vector containing the *env* gene of feline leukemia virus (FeLV), encoding the gp70 protein. Although the gene was expressed in vaccinated cats and mice, no anti-gp70 antibodies

were detected in the serum of vaccinated animals, indicating a clear lack of immunogenicity. In contrast, Wardley demonstrates a decisive protective immunogenic response against FeLV using a recombinant herpesvirus vector containing the FeLV *env* gene. This directly supports the argument that poxviruses and herpesviruses are not analogous vaccine vectors, as they produce disparate results using the same immunogen, *i.e.* the herpesvirus-based vaccine elicited a protective immune response, while the poxvirus-based vaccine did not.

In summary, Gilbert shows that an immunogenic response against feline leukemia virus (FeLV) was not elicited in cats or mice vaccinated with a recombinant vaccinia virus (i.e. poxvirus) vector expressing the FeLV *env* gene. In contrast, a protective response was demonstrated by Wardley in cats vaccinated with a recombinant herpesvirus vector expressing the same gene. These studies are evidence is support of Applicants' position that one cannot extrapolate from one viral vector system to another with an expectation of success. The Examiner is respectfully reminded that "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). Therefore, Paoletti cannot be properly combined with Haanes as the basis for an obviousness rejection.

An abstract by Xuan *et al.*, demonstrating the efficacy of the claimed invention, is attached. Xuan shows an immunogenic response to rabies virus, using a recombinant CHV containing the nucleic acid sequence encoding rabies virus G protein. Significantly, it shows that the antibody titers are higher than those elicited by a commercial vaccine containing inactivated rabies virus. Therefore, not only is the instant invention unexpectedly successful, it also shows suprisingly superior results over classical vaccines.

Claims 17-28, 33, 34 and 38-49 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over Haanes *et al.* (U.S. Patent No. 5,753,235 or 5,804,197), in view of Cates *et al.* (WO 97/11093). The deficiencies of Haanes are discussed above. Cates relates to the use of HN and F proteins from parainfluenza virus in vaccines. The claims are not directed to proteins from parainfluenza virus; therefore, there is nothing in the combination of Haanes *et al.* and Cates *et al.* that teaches or suggests the claimed invention.

Claims 17-28, 35, 36 and 39-49 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over Haanes *et al.* (U.S. Patent No. 5,753,235 or 5,804,197), in view of Barbour *et al.* (U.S. Patent No. 5,777,095). Barbour *et al.* characterizes the genes encoding OspA and OspB, which are not recited in the pending claims.

Accordingly, the instant invention is not *prima facie* obvious. None of the cited references, alone or in combination, teach or suggest the desirability and efficacy of a recombinant CHV comprising and expressing at least one heterologous nucleotide sequence encoding rabies virus G antigen. Therefore, reconsideration and withdrawal of the rejections under §103(a) are requested.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance, or at least in better condition for appeal. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date.

Respectfully submitted,

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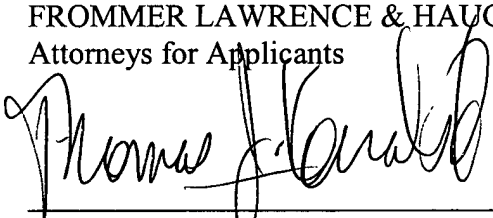

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